The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry

Draft Guidance – Not for Implementation

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Center for Devices and Radiological Health

Office of Device Evaluation

Preface

Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. 01D-0202, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

I. Background

A central purpose of the Food and Drug Administration Modernization Act of 1997 (FDAMA) is "to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development."[1] As can be seen in this statement, Congress' goal was to streamline the regulatory process (i.e., "reduce burden"[1]) to improve patient access to breakthrough technologies. It is equally clear from the legislative history, however, that while Congress wanted to reduce unnecessary burdens associated with the premarket clearance and approval processes, Congress did not intend to lower the statutory thresholds for substantial equivalence or reasonable assurance of safety and effectiveness.

To help achieve this goal, Congress added sections 513(a)(3)(D)(ii) and 513(i)(1)(D) to the Federal Food, Drug, and Cosmetic Act (the act). These provisions capture both of the ideas expressed in the legislative history: FDA should eliminate unnecessary burdens that may delay the marketing of beneficial new products, but the statutory requirements for clearance and approval remain unchanged.

Specifically, section 513(i)(1)(D) states, "Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such a request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly." Section 513(a)(3)(D)(ii) states that, "Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

[1] Senate Report No. 105-43 (1997).

These two sections of the law contain what are commonly referred to as the "least burdensome provisions" of the act. Over the last few years, FDA has been working to develop an interpretation of the least burdensome provisions that would accurately capture Congress' intent and that could be implemented consistently by FDA and industry. This guidance is one part of that process. As presented below, FDA has chosen to apply the least burdensome concept beyond the two statutory provisions in which the language actually appears. FDA considers the least burdensome concept to be one that could affect almost all premarket regulatory activities, including presubmission meetings with industry, premarket submissions, and the development of guidance documents and regulations. The Agency believes that this interpretation most accurately reflects the spirit of the new law.

In order for the broad approach to be successful, it is important that industry continue to meet all of its statutory and regulatory obligations. It is also important that FDA continue to enforce the statutory and regulatory provisions that are in place to protect the public after a device reaches the market. The confidence that the American public and the global market place on FDA regulation relies on inspections, surveillance, and reporting activities as much as on premarket review. If FDA becomes aware of information unrelated to the clearance or approval decision, but which could represent noncompliance with the law or its implementing regulations, such issues cannot be ignored. While FDA will not withhold the clearance or approval decision because of an issue unrelated to a premarket decision, all FDA staff have a responsibility to share information that may require regulatory or enforcement follow up so that the Agency can enforce its statutory and regulatory authorities in the postmarket period.

Finally, although the least burdensome provisions are recent additions to the statute, it should be recognized that there are cases in which the Agency has utilized a least burdensome approach in resolving a regulatory issue or in helping industry to bring a new device to market. In fact, several examples of situations in which the Agency used the least burdensome approach are presented in this guidance. By adding these provisions to the act, however, FDA recognizes that Congress was directing the Agency to implement this type of approach in a consistent and uniform manner to encourage the timely development of new technologies. FDA believes that this guidance, in combination with other guidances that have been developed as a part of the least burdensome effort, will help to ensure that the Agency accomplishes this important goal.

II. What does "Least Burdensome" Mean?

We are defining "Least Burdensome" as **a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA.** This concept applies to all devices and device components of combination products regulated by FDA (including *in vitro* diagnostics (IVDs)) and, when conscientiously applied, will help to ensure scientific integrity in the decision-making process, while affording a high degree of public health protection and expediting the availability of new device technologies. The Least Burdensome concept should be integrated into all premarket activities as well as postmarket activities, as they relate to the premarket arena. These activities include:

- Simple inquiries regarding device development
- Pre-submission activities, including early collaboration meetings and the Pre-IDE process

- Premarket submissions
- Panel review and recommendations
- Post-approval studies
- Reclassification petitions
- Guidance document development and application
- Regulation development

III. What Basic Principles Underlie the Least Burdensome Concept?

FDAMA did not change the statutory threshold for premarket clearance or approval. To continue to meet this standard, while also fulfilling the intent of the Least Burdensome provisions of FDAMA, we have identified the following basic principles:

- The spirit and the letter of the law, as well as sound science, should be the basis for all regulatory decisions;
- Information unrelated to the regulatory decision should not be part of the decision-making process;
- Alternative approaches to regulatory issues should be considered to optimize the time, effort, and cost of reaching resolution of the issue within the law and regulations; and
- All reasonable measures to lessen review times and render regulatory decisions within statutory timeframes should be used.

IV. How do the Least Burdensome Principles Apply to PMAs (Originals and Supplements)?

FDA and industry should focus on the statutory criteria for approval of the PMA, i.e., the determination of reasonable assurance of safety and effectiveness, as defined in the regulations (21 CFR 860.7). This determination should be based on valid scientific evidence, and information unrelated to the premarket approval decision should not be submitted to, nor requested by, the Agency. Hyperlink #1

Where clinical outcome can be predicted from non-clinical data, well-designed bench and/or animal testing can be the basis for approval of the PMA. Conditions where non-clinical data may meet the threshold for approval are typically those devices or modifications of approved devices for which information is available in the public domain. If clinical data are needed, FDA and industry should consider alternatives to randomized, controlled clinical trials in those situations when potential bias associated with alternative controls can be addressed.

Given the above, alternative approaches may include:

- Reliance on valid[2] non-U.S. data (where appropriate for the intended U.S. patient population),

[2] 21 CFR 814.15(b) indicates that for FDA to accept studies conducted outside the U.S. in support of a PMA, the data must be "valid."

- "Paper PMAs,"[3] or
- Study designs employing non-concurrent controls such as historical (e.g., literature, patient records), objective performance criteria (OPC)[4], and patients as their own control. Hyperlink #3

In addition, when clinical data are needed for PMA approval, the use of scientifically valid surrogate endpoints (Hyperlink #4a) and statistical methods, such as Baysian analyses,[5] should be considered. If incorporated as part of the study design, early submission of the application may also be considered, as appropriate. Hyperlink #4b

Whenever possible, FDA and industry decisions about device development and review should rely on information that is available from earlier versions of the same device or from marketing experience with similar devices. Recognizing that devices often develop incrementally, earlier generations of a product line may provide important information to reduce the need for new data. In addition, information gathered throughout a product's life cycle can also reduce data requirements.

The role of postmarketing information should be considered in determining the appropriate type/amount of data that needs to be collected in the premarket setting to support PMA approval. Postmarketing information should also be considered for assuring long-term device safety and effectiveness, wherever appropriate. Discussions regarding the premarket/postmarket balance should occur early in the device development process with the understanding that the threshold for approval continues to be reasonable assurance of safety and effectiveness. Hyperlink #5

The effective use of FDA-recognized standards can streamline PMA submissions and provide for a more efficient review process. Declarations of conformity to these standards should be submitted whenever possible. Hyperlink #6

V. How do the Least Burdensome Principles Apply to 510(k)s?

FDA and industry should focus on those issues that can affect the substantial equivalence (SE) determination, that is, whether the device has the same intended use as the predicate device and is as safe and effective as a legally marketed device. Information unrelated to the substantial equivalence decision should not be submitted to, nor requested by, the Agency. Hyperlink #7

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[3] A "paper PMA" is one that is based on bench testing and/or information derived from peer-reviewed scientific literature. For example, a paper PMA may rely on a meta-analysis of information derived from the literature. Hyperlink #2

[4] "Objective performance criteria" are performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values. These criteria may be used for surrogate or clinical endpoints and may be used in the demonstration of safety or effectiveness of the device.

[5] Modern statistical methods may also play an important role in achieving a least burdensome path to market. For example, through the use of Baysian analyses, studies can be combined to help reduce the sample size needed for the experimental and/or control device.

In assessing the use of the device for purposes of the SE determination, labeling should be reviewed to ensure that the necessary elements identified in 21 CFR 807. 87(e) (i.e., device description, intended use, and directions for use) are adequate and not misleading. Ensuring compliance with other regulations (e.g., 21 CFR Parts 801 (except for 801.6), 809, 820) should not ordinarily be part of the SE determination. Hyperlink #8

In making the SE determination, the Center should reaffirm its longstanding review policy[6] that:

(1) Substantial equivalence will normally be determined based on comparative device descriptions, including performance characteristics; and
(2) Performance testing should be submitted if there are important descriptive differences between the device and other devices of the same type or the descriptive characteristics for the new device are not precise enough to assure comparability. In these instances, the most appropriate bench and/or animal testing, or in the case of IVDs, analytical testing, to address the performance issue should be provided. Summary information regarding the testing should generally suffice, but the test protocol, description of test methods, or any standards followed in conducting the testing should also be provided.

Given that clinical data are not required for most 510(k)s, the Agency should clearly document the issue that warrants clinical data. In deciding how the clinical data should be obtained, FDA and industry should consider alternatives to randomized, controlled clinical trials, as discussed above for PMAs, in those situations when potential bias associated with alternative controls can be addressed. Alternatives such as reliance on valid[2] non-U.S. data (where appropriate for the intended U.S. patient population), use of meta-analyses, and trial designs employing non-current controls such as historical (e.g., literature, patient records), OPC, and patients as their own control should be considered. In addition, the use of scientifically valid surrogate endpoints should be considered as discussed above for PMAs. Hyperlink #9

In accordance with the guidance document entitled, "Guidance for Industry and FDA Staff – Use of Standards in Substantial Equivalence Determinations,"[7] industry should submit and FDA should rely on a manufacturer's: 1) statement that a device will meet a recognized standard or 2) a declaration of conformity to a standard, as appropriate**.** Hyperlink #10

FDA should not request information regarding changes observed in a new 510(k) that were previously implemented by industry without the requirement for 510(k) clearance unless the lack of information regarding the previous modification(s) does not allow the SE determination to be made. Hyperlink #11

Manufacturing information should not be part of a 510(k) submission unless the information relates to the equivalency determination. Hyperlink #12

[6] "Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program." June 30, 1986. (www.fda.gov/cdrh/k863.html)
[7] This guidance is available on the web at: www.fda.gov/cdrh/ode/guidance/1131.html

VI. What are Some General Applications of the Least Burdensome Principles?

FDA and industry should utilize a *Systems Approach*[8] to device regulation and take full advantage of all regulatory tools available through FDAMA and reengineering, such as the *de novo* risk-based classification process and "*The New 510(k) Paradigm*." Hyperlink #13 The reclassification and exemption processes should also be used to ensure that the proper level of regulatory control is applied to a device type. Hyperlink #14

Reliance on postmarket controls (e.g., compliance with the Quality Systems (QS) regulation, postmarket surveillance, and the Medical Device Reporting requirements) should be considered as a mechanism to reduce the premarket burden for 510(k)s and PMAs while still ensuring the safety and effectiveness of the device. Hyperlink #15

FDA and industry should make effective use of well-designed bench and/or animal testing. When non-clinical testing is being conducted or requested, the testing should be designed to address a specific question, use standards or standardized test methods whenever possible, employ scientifically relevant end-points, and use an appropriate bench and/or animal model. Hyperlink #16

Industry should incorporate by reference other premarket submissions, whenever possible. FDA should encourage and accept this practice as a means of saving resources. Hyperlink #17

FDA should generally avoid using premarket review to ensure compliance with FDA statutes or regulations unrelated to the regulatory decision (e.g., Radiation Control for Health and Safety Act (RCHSA), QS regulation). Similarly, verifying compliance with laws and regulations administered by other federal agencies (e.g., Occupational Safety and Health Administration (OSHA)) should not ordinarily be part of the substantial equivalence or approval decision. Hyperlink #18

When requesting additional information to resolve a regulatory issue, FDA should:

- Identify the specific issue or question that the request is attempting to address;
- Acknowledge information submitted and why the information is deficient;
- Establish the relevance of the request to the determination that is being made, i.e., substantial equivalence or reasonable assurance of safety and effectiveness; and
- Remain open-minded to alternate ways to address the issue or question. Hyperlink #19

In responding to the FDA's request for additional information, industry should make every attempt to respond completely and promptly. The response should:

- State the Agency issue, and
- Provide one of the following:

[8] "A Systems Approach to Premarket Review" can be found at: www.fda.gov/cdrh/ode/guidance/prerevapproach.html

- the information requested, or
- an explanation why the issue is not relevant to substantial equivalence or safety and effectiveness, or
- alternative information and an explanation of why the information adequately addresses the issue. Hyperlink #19

Whenever possible, FDA and industry should attempt to resolve minor questions/issues by phone, fax, or e-mail. FDA should use deficiency letters to resolve the more complicated issues (i.e., major deficiencies) and include only those minor deficiencies that have not been adequately addressed by phone, fax, or e-mail. Industry should promptly respond to questions regarding minor deficiencies to avoid unnecessarily prolonging the review time. When FDA receives the additional information, the Agency should determine the relevancy and adequacy of the information to the SE or approval decision. Similarly, if industry proposes an alternative approach to resolving a regulatory issue, FDA should review the appropriateness of the proposed alternative and, if needed, discuss it with industry.

If industry believes that the Agency did not use the Least Burdensome approach in attempting to resolve a regulatory issue, there are several avenues available. In addition to the longstanding mechanisms available through supervisory oversight, CDRH has appointed a Center ombudsman who is also available as a resource to help resolve least burdensome issues.[9]

The least burdensome principles should also be applied in the development of guidance documents and regulations. Hyperlink #20a; Hyperlink #20b

VII. Conclusion

Full implementation of the least burdensome provisions of FDAMA is critical to, but only a part of, achieving Congress's intent in passing the new law. Application of the least burdensome principles to premarket requirements will help to reduce regulatory burden and thus save Agency and industry resources. In order to achieve Congress' goal to "ensure that the FDA is an agency committed to fostering innovation and ensuring timely public access to beneficial new products,"[1] however, a least burdensome approach should be used in almost all regulatory activities, including those in the postmarket arena. In addition, both FDA and industry should fully utilize all regulatory mechanisms provided by the law, the implementing regulations, Agency policies, and the Center's recent reengineering efforts.

[9] "A Suggested Approach to Resolving Least Burdensome Issues" can be found at: www.fda.gov/cdrh/ode/guidance/1188.html

Hyperlinks

Hyperlink #1

As defined in Section 515 of the act, the criteria for approval of a PMA is "reasonable assurance that a device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Reasonable assurance of safety is defined in 21 CFR 860.7(d)(1) as "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."

Reasonable assurance of effectiveness is defined in 21 CFR 860.7(e)(1) as "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

"**Valid Scientific Evidence** is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use." (21 CFR 860.7(c)(2))

In accordance with the Least Burdensome principles, information unrelated to the premarket approval decision should not be submitted to, nor requested by, the Agency. General examples of such information include the results of consumer preference testing and cost-effectiveness studies. As a specific example, consider the issue of electromagnetic compatibility (EMC). In the early 1990's, FDA was just becoming aware of the issue of electronic interference with medical devices. Recognizing the tendency to ask industry to address the issue of EMC in PMAs, the Center issued guidance[10] to the review staff on the proper way to approach EMC. This guidance stated that individual approval decisions should not be withheld based on EMC concerns when other legally marketed devices of the same type pose the same concern. In other words, in situations where a new issue surfaces that affects all devices of a type, it is important to deal with all of the devices that present that concern rather than hold up a specific application.

[10] "Electromagnetic Compatibility for Medical Devices: Issues and Solutions" can be found at: www.fda.gov/cdrh/ode/639.pdf

Hyperlink #2

For marketing applications based solely on information in the literature, the relevance and adequacy of the information needs to be determined. To help determine how successful a particular body of literature will be in supporting the clearance/approval of a new device, the adequacy of the study design needs to be assessed, and questions such as those listed below need to be considered:

- Is the device in the literature of comparable technology to the device under consideration for clearance/approval?
- Was the device in the literature intended to provide the same diagnostic or therapeutic intervention? For the same disease/condition? For the same patient population?
- Was the device used in a patient population that is adequate to represent the target population for the new device?
- Does the literature contain an adequate description of the protocol/procedures, including details of device use, follow-up, and safety and effectiveness endpoints for the stated indication?
- Is the patient accounting information in the literature sufficient to determine how the device performed?

Finally, when deciding if an article could be used in support of marketing of a new device, FDA and industry should consider contacting the author(s) of the research for additional information. For example, the study methods described in the literature are often are very concise and do not include important details, such as the randomization method. Clarifying such information may be accomplished by contacting the author(s), thus, allowing the article to be used in support of the marketing application.

Hyperlink #3

Where clinical outcome can be predicted from non-clinical data, well-designed bench and/or animal testing can be the basis for approval of the PMA. Conditions where non-clinical data may meet the threshold for approval are typically those devices or modifications of approved devices for which information is available in the public domain. FDA and industry should consider alternatives to a randomized, controlled trial (RCT) in those situations when potential bias associated with alternative controls can be addressed. While alternatives to a randomized, controlled trial should be considered, it should not be assumed that an RCT would be more costly in terms of both time and money. Industry should be aware that, in general, smaller sample sizes and less elaborate statistical analyses are needed for RCTs than for alternative trial designs. A major advantage of the RCT design is the assurance that confounding factors, such as selection biases, will be minimized by the randomization, thus facilitating a more timely review of the data.

For some diseases/conditions, however, alternative study designs to traditional RCTs may be appropriate. For example, if there is no satisfactory intervention for the disease/condition being studied or if only a limited number of patients are available to be studied, sponsors may consider a cross-over design or whether patients could serve as their own baseline control. In other cases,

validated objective outcomes or historical information from the literature may be available to allow for studies without a concurrent control. Finally, if an RCT is used, randomizing more often to the experimental device than the control therapy can reduce the burden of an RCT. Given the unique aspects often presented by device clinical studies, industry and FDA should consider all available options to ensure that the most appropriate, but also the least burdensome, approach is used.

Below are some examples of when a PMA supplement or an original PMA were approved using alternatives to RCTs as the least burdensome approach:

Modifications to the arrhythmia detection algorithm for an approved implantable cardioverter defribillator were proposed to allow the device to discriminate between atrial and ventricular arrhythmias. Because it was determined that bench testing would allow a more thorough analysis of the change than a clinical trial, bench testing using pre-recorded human heart ECGs and an observational post-approval study were used to support approval of the PMA supplement.

A PMA was approved for a pneumatic ventricular assist device (VAD). The company wished to modify the device to be electrically controlled. The Agency relied primarily on bench testing to demonstrate that the flow pattern and cardiac index remained unchanged. Limited clinical data were collected to confirm that the type and frequency of adverse events were also unchanged.

FDA approved modifications to a thermal ablation device, including hardware, software, and operational system changes, based on laboratory data and an engineering design analysis.

Patient registries and literature were used to support the approval of a PMA for a bone cement for fixation of a hip prosthesis. Similarly, several orthopedic implants (constrained acetabular liner and cemented finger joint) were approved using data in the literature.

PMAs for a cochlear implant and a sacral nerve stimulator for urinary incontinence were approved using studies in which the patients served as their own control.

A "paper" PMA was approved for a contact lens. Clinical data reported in the Japanese literature were used to support the application.

Hyperlink #4a

Scientifically valid surrogate endpoints should be used whenever appropriate to reduce the premarket burden. This type of endpoint is used routinely by the Agency for many implanted devices, such as orthopedic prostheses, implantable cardioverter defibrillators, stents, and vascular grafts. Almost all approvals of these types of implants are based on short-term (1 or 2 year) data as a surrogate for long-term experience. Other specific examples in which FDA has relied on scientifically valid surrogate endpoints include the PMA for digital mammography. To expedite the availability of this new imaging modality, FDA relied on sensitivity and specificity measurements of the detection of the presence/absence of breast cancer as surrogate endpoints

for the new device rather than using the clinical endpoint of the reduction in mortality due to breast cancer. Presuming that the detection of breast cancer has clinical benefit even if it is not directly linked to a reduction in mortality allowed the clinical trial to be conducted in a least burdensome manner but still ensured that the statutory threshold for approval was met.

As another example of the use of surrogates, consider the approval of a low density lipoprotein (LDL) column. This column was approved for patients with certain risk factors based on high LDL levels. For this device, the reduction of the cholesterol level was used as a surrogate for reducing the risk of atherosclerotic complications. For IVDs, surrogates have been used in clinical studies of tumor markers for the early detection of cancer as well as in studies of cardiac markers, such as troponin I and T analytes. Another example is the use of spinal flexion and extension, as viewed on plain film x-rays, as surrogate endpoints for fusion in studies of spinal cages.

Hyperlink #4b

Under certain predetermined conditions, a PMA may be submitted before all of the patients are followed according to the investigational plan. For example, if the statistical analysis includes an interim analysis with predetermined criteria for stopping the study, the application may be submitted early if the analysis demonstrates that the criteria for the early stopping were met. In other cases, the Agency has permitted some PMAs to be submitted when a pre-specified number of patients had been followed in accordance with the investigational plan. Data on the remaining patients were submitted post-filing as a PMA amendment. This latter situation has normally been decided on a case-by-case basis. It should be noted that an unplanned early submission of data could create evaluation difficulties. Therefore, FDA recommends that if a sponsor is considering submitting a PMA before the full cohort of patients has been followed according to the investigational plan, the firm should discuss its plan with the Agency.

Hyperlink #5

The role of postmarketing information should be considered in determining the appropriate type/amount of data that needs to be collected in the premarket setting to support PMA approval. These discussions should occur early in the device development process rather than when approval of the application is being decided. Discussions between FDA staff and industry may be informal and occur as a part of the pre-IDE process (www.fda.gov/cdrh/ode/d99-1.html). Alternatively, they may be more formal and be a part of the early collaboration Agreement/Determination meeting process (www.fda.gov/cdrh/ode/guidance/310.pdf). To illustrate how postmarketing information may be used to help decide what type of data is needed for PMA approval, consider the decision with regard to brachytherapy for the reduction of in-stent restenosis. In recognition that long-term information on the effect of radiation on the restenosis rate and the incidence of thrombosis was needed, a postmarketing trial was agreed upon during the approval process. This least burdensome approach allowed patients to have access to this promising new technology but also permitted FDA to gain long-term safety and effectiveness data. Similarly, a biliary lithotriptor was approved for marketing with data demonstrating that the device could break up biliary stones. Postapproval data will be collected

to demonstrate that the device, in combination with drug therapy, results in improved clinical outcome.

Hyperlink #6

The Center has recognized over 500 voluntary consensus standards. (For a searchable database of standards, see www.fda.gov/cdrh/stdsprog.html). Some of these standards relate to individual products while others address crosscutting issues such as electrical safety, sterilization, and biocompatibility. For example, FDA has recognized 28 voluntary consensus standards that address numerous aspects of wheelchair performance. While most wheelchairs are Class II devices, many of these standards are applicable to the Class III stair climbing wheelchairs. Other device–specific standards include the ISO standards for heart valves and vascular grafts and the NCCLS standards that apply to most *in vitro* diagnostic devices. Cross-cutting standards, such as the IEC electrical safety and ISO sterilization standards, apply to numerous device types reviewed by FDA. Declarations of conformity to standards that identify test methods can reduce the detail needed in PMA submissions and eliminate FDA review of test procedures. Use of those standards that have performance criteria can further reduce data reporting requirements in the application and save Agency review time.

Hyperlink #7

The purpose of a 510(k) submission is to determine whether the device is "substantially equivalent" to a predicate device. Section 513(i) of the act establishes the conditions under which devices can be determined to be "substantially equivalent." This section of the act states that FDA may issue an order of substantial equivalence only upon making a determination that the device to be introduced into commercial distribution has the same intended use as the predicate device and is as safe and effective as a legally marketed device.

Information unrelated to the substantial equivalence determination should not be requested or reviewed by the Agency. As with PMAs, this would normally include information related to cost-effectiveness and consumer preference testing. In addition, it would include information related to scientific curiosity. As an example, consider a device-specific guidance document for diagnostic ultrasound. This guidance was modified in accordance with the least burdensome approach to remove the routine submission of Doppler sensitivity test results unless the submitter wished to make quantitative statements in the labeling about the sensitivity.

Hyperlink #8

The 510(k) process is not a mechanism for ensuring compliance with all FDA regulations that may apply to a particular device. Manufacturers of 510(k) devices are required to comply with a number of regulations, including the labeling requirements in 21 CFR 801 (and 809.10 for IVDs) as well as the good manufacturing requirements in Section 820. To illustrate a proper 510(k) review of a device where other FDA regulations have applicability, such as those previously listed, consider the following least burdensome approach to the review of labeling. In accordance with 21 CFR 807.87(e), a 510(k) submitter should provide “proposed labels, labeling, and advertisements sufficient to describe the device, its intended, and the directions for

its use." While 21 CFR 801 contains specific requirements with which 510(k) holders must comply, ensuring compliance with this regulation should not be part of the SE determination. Instead, FDA should focus its 510(k) review on those aspects of the labeling required by section 807.87(e) (i.e., description of the device, its intended use, and the instructions for use) or labeling that is serving as a special control. In assessing the use of the device for purposes of the SE determination, FDA should ensure that the required sections of the labeling are adequate and not misleading.

Similarly, 21 CFR 809.10 governs the labeling for in vitro diagnostics (IVDs) and specifies very detailed information that is to be included in the labeling for all IVDs. It should be recognized, however, that 21 CFR 809.10 applies not only to IVDs undergoing review by FDA in 510(k) submissions, but also to the numerous Class I and II IVDs that are exempt from 510(k) requirements. A least burdensome approach to the 510(k) review of IVDs would rely on the industry's legal obligation to meet the requirements of 21 CFR 809.10. FDA would focus its review of the labeling on the required elements identified in 21 CFR 807.87(e) as discussed above. This least burdensome approach to the review of labeling in IVD 510(k)s would not interfere with FDA's ability to obtain whatever data or information is necessary to make the SE determination. The Agency should be careful, however, to distinguish between information needed for the SE determination and information needed to make complexity designations in accordance with the Clinical Laboratory Improvement Act (CLIA).

Hyperlink #9

Given that clinical data are not required for most 510(k)s, the Agency should clearly document the issue that warrants the clinical data. In addition, FDA should work with industry to identify the type and extent of data that will be required for clearance. For example, clinical data may be needed to address how a new material will wear when exposed to physiological loading in humans. In this case, FDA should explain why animal testing would not be sufficient and work with the company to identify the type and extent of the data that will be needed. This would include parameters such as the number of patients, endpoints, and length of follow-up.

When designing the clinical study, as discussed above for PMAs, FDA and industry should consider alternatives to RCTs. Below are examples of recent SE determinations that relied on alternative study designs:

> To support the clearance of a Hepatitis A diagnostic test, FDA requested a prospective clinical study be conducted using patient serum and plasma samples with elevated levels of lipid, hemoglobin, and bilirubin. Industry proposed a least burdensome alternative approach. In their proposal, which was accepted by FDA, interference testing would be conducted by adding known concentrations of lipid, hemoglobin, and bilirubin to banked serum and plasma samples (i.e., spiked samples) and comparing these results to the testing conducted on unspiked samples.
>
> To support the clearance of an electrosurgical device for a specific medical indication, the Agency requested a side-by-side comparison of the investigational device and a predicate device on extirpated human tissue. Industry proposed that an animal model, which is the

established standard for such performance testing for this type of device, be used rather than human tissue. FDA agreed to accept data from the valid animal model.

Hyperlink #10

To illustrate the effective use of FDA recognized standards in the review process, consider the Agency's guidance document entitled, *"Latex Condoms for Men: Information for 510(k) Premarket Notifications: Use of Consensus Standards for Abbreviated Submissions"* (www.fda.gov/cdrh/ode/92_b.html). The Agency's approach to demonstrating substantial equivalence for latex condoms relies heavily on conformance to several recognized voluntary standards. Rather than submitting performance data for review in the 510(k), the approach stressed in this guidance document is to do the testing required by the recognized standards and to submit Declarations of Conformity to the standards. This approach not only supports the use of standards as intended by FDAMA, but also takes advantage of the Abbreviated 510(k) option created under "The New 510(k) Paradigm."[11] This example shows how standards may be effectively used in a guidance document.

As a second example of how FDA has incorporated the use of standards in the 510(k) process, consider how the Agency has relied on the requirements of the Radiation Control for Health and Safety Act (RCHSA). 21 CFR 1050 establishes federal performance standards under RCHSA for non-ionizing radiation diagnostic devices. In the past, data demonstrating conformance with these standards have routinely been submitted in traditional 510(k)s. Recently, the reviewing division provided guidance that encourages industry to submit a certification that the appropriate testing has been completed in accordance with the FDA recognized standards rather than submitting the supporting data in a 510(k).

Hyperlink #11

Under the guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device,"[12] 510(k) holders have considerable latitude in making modifications to their legally marketed devices without the need for submitting new premarket notifications. According to this guidance, 510(k) holders assess whether a labeling, technology/performance specification, or materials change requires the submission of a new 510(k) using the flowcharts in the document. If the manufacturer determines that, based on a comparison of the modified to device to an earlier version of the device for which Agency clearance was obtained (or to their preamendments device), a new 510(k) is not needed, the manufacturer maintains records of its decision-making process.

This latitude creates some difficulties for FDA when assessing a 510(k) for a device that has been modified during the product life cycle but is now being modified in a way that requires 510(k) clearance. A least burdensome approach to such a situation would involve focusing on

[11] This guidance can be found at: www.fda.gov/cdrh/ode/parad510.html
[12] This guidance can be found at: www.fda.gov/cdrh/ode/510kmod.html

the information that relates exclusively to the modification that triggered the need for a new 510(k). Given that device performance may depend on many aspects of overall device design, not just the change that is the subject of the new 510(k), there will be instances where testing of the overall device design is necessary to render a finding of substantial equivalence. In these instances, the reviewer's focus should be on the testing that is necessary to ensure that the overall device is as safe and effective as a legally marketed predicate. That is, industry could present data to compare the modified device that triggered the new 510(k) submission with an earlier version of the device that represents a series of changes that by themselves did not require 510(k) review, or the submitter could claim equivalence to a competitor's legally marketed device. In either case, the least burdensome approach would be one in which FDA focuses on the overall performance of the device in making the substantial equivalence determination rather than on the review of all of the intermediate changes that did not require 510(k) submission.

Hyperlink #12

Manufacturing information should not be part of a 510(k) submission unless the information relates to the equivalency determination. By design, the 510(k) process focuses primarily on the end product of the manufacturing process rather than the manufacturing process itself. The Quality Systems (QS) regulation requires device manufacturers to perform design verification and validation testing, as appropriate, on new devices as well as on modifications to existing devices. FDA should ask, however, only for the testing that is necessary to make an equivalency determination. For example, in special 510(k)s, manufacturers submit design control information to establish substantial equivalence. Routine submission and review of design verification and validation data performed and maintained in accordance with the QS regulation can delay review of the 510(k) by leading to questions that do not relate to determining substantial equivalence.

To further illustrate this point, consider ODE's current policy regarding sterilization. For "traditional" methods of sterilization, submitters of 510(k)s need only provide a brief description of the method of sterilization and the sterility assurance level (SAL) (www.fda.gov/cdrh/k90-1.html). Quality Systems requirements help to ensure that final finished devices meet their release specifications and thus have been properly sterilized. For "non-traditional" methods of sterilization, current review practices frequently call for the submission of process verification and validation data that demonstrate that the final devices meet their release specifications. A least burdensome approach to sterility in 510(k) submissions would be to rely on a manufacturer's legal obligation to comply with the Quality Systems requirements, including the assurance of the sterility of finished devices, regardless of the method of sterilization that a manufacturer chooses to employ. Sterility of the finished device is addressed through the regulatory requirement that a manufacturer conducts proper process verification and validation studies that ensure the adequacy of the manufacturing processes to produce the specifications described in the manufacturer's 510(k). This approach is consistent with that presented in Hyperlink #1 where it is stated that if FDA has a concern that would apply to all devices of a type or to many different types of devices, the issue should be addressed for all of the affected devices rather than holding up an individual application.

Hyperlink #13

FDAMA and reengineering provided the Agency and the industry with a variety of tools which can be used to lessen the regulatory burden. Consider new Section 513(f)(2) of the act entitled, "Evaluation of Automatic Class III Designation," commonly referred to as the *de novo* process (www.fda.gov/cdrh/modact/classiii.html), and what it can afford when combined with the opportunities created through 510(k) reengineering efforts, such as the creation of "The New 510(k) Paradigm."[11] The *de novo* process has been successfully used many times. In each case, it was determined that either general controls alone, or general controls combined with special controls, could ensure the safety and effectiveness of the new device, thus avoiding the more burdensome PMA process. The *de novo* process, when combined with the opportunity for 510(k) exemption and the flexibility created by "The New 510(k) Paradigm," creates an effective mechanism for matching the necessary regulatory controls to the risks of the device. As an example, consider the new generation of surgical instruments that represent computer-assisted versions of traditional devices. Surgical instruments are for the most part Class I 510(k) exempt devices. Significant changes in technology could easily place these devices in Class III subject to PMA. Where there is a clear understanding of the risks that are inherent with these new surgical technologies and special controls can be developed to address them, FDAMA's *de novo* process would allow FDA to place these types of devices in Class II subject to general and special controls. This classification, when combined with the use of voluntary consensus standards and conformance with design controls under the QS regulation, could permit new and modified devices to get to market in a least burdensome manner.

As a specific example of how "The New 510(k) Paradigm" can be used to reduce regulatory burden, consider a design change to a class II electrophysiology (EP) catheter. A 510(k) holder of a legally marketed EP catheter wanted to alter the shape of the curve of the device. After conducting a risk analysis of the change and completing certain design verification/validation activities required under the QS regulation, the company concluded that the redesigned device was as safe and effective as its marketed device. After considering the alternative approaches presented in The New 510(k) Paradigm, the company determined that a Special 510(k) represented the least burdensome approach to getting clearance for the EP catheter and, therefore, submitted this type of 510(k) for the change.

Hyperlink #14

The reclassification and exemption processes should be used to ensure that the proper level of regulatory control is applied to a device type. The Safe Medical Devices Act of 1990 (SMDA) and FDAMA, by facilitating the reclassification and exemption processes, reinforced the Medical Device Amendments of 1976 directive to continue to consider the lowest appropriate level of regulatory control sufficient to ensure safety and effectiveness of the device. As a result, FDA has reclassified numerous devices, including many preamendments Class III devices, into Class II. In other cases, special controls have been used to streamline the 510(k) process by allowing Class II devices to be exempt from the premarket notification requirements. While the Agency should continue to look for reclassification opportunities, industry also should take advantage of these tools and submit reclassification petitions and/or exemption requests when

appropriate. Guidance[13] is available to help industry in developing requests for 510(k) exemption. Wise use of general and/or special controls could allow certain devices to be downclassified and perhaps even made 510(k) exempt, while still ensuring the safety and effectiveness of the device.

Hyperlink #15

Since SMDA, FDA has been challenged to rely on postmarket controls to reduce the premarket burden for all classes of devices. In FDAMA, however, Congress made its intention explicit by adding two new sections to the statute. Specifically, new section 513(a)(3)(C) states, "…the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls." Similarly, new section 513(i)(1)(C) states, "To facilitate reviews of reports submitted to the Secretary under section 510(k), the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices …."

The postmarket controls to which the statute is referring include controls such as the QS regulation, postmarket surveillance, and the Medical Device Reporting (MDR) requirements. For 510(k)s, "The New 510(k) Paradigm"[11] advocates relying on design controls, a critical part of the QS regulation, to address certain design modifications. Under The Paradigm, changes that do not affect the fundamental scientific technology or intended use of the device may be submitted as Special 510(k)s. For these well-defined modifications, "the Agency believes that the rigorous design control procedure requirements produce highly reliable results that can form, in addition to the other 510(k) content requirements …, a basis for the substantial equivalence determination." Thus, for Special 510(k)s, industry submits a summary of their design control activities and a declaration of conformity to design controls, but the data generated as a result of the design control procedures are maintained by the manufacturer and not submitted to the Agency. Examples of changes permitted through the Special 510(k) option include replacing a polyurethane coating with a silicone coating on an electrode, adding a scanner to a Er:YAG laser, and adding a new algorithm to an EEG to assist in test data interpretation. In each of these instances, manufacturers conducted verification and validation testing, as appropriate, to support the device modification. Results of the testing are maintained by the manufacturer but are available for FDA inspection. Thus, use of this postmarket control can significantly reduce the premarket burden and, as indicated in the statute, "expedite the classification of devices."

In addition to the use of design controls in a specific manner such as Special 510(k)s, it is important to note a broader and more fundamental aspect of design control requirements. As indicated in the human factors guidance document,[14] human factors are an important consideration in a device manufacturer's quality assurance program, particularly the design control section of the QS regulations. The implementation of good human factors practices, through the design control requirements, can help to ensure that medical devices are as safe and effective as reasonably possible. Identifying and addressing issues associated with safe device

[13] "Procedures for Class II Device Exemptions from Premarket Notification" can be found at: www.fda.gov/cdrh/modact/exemii.html.
[14] "An Introduction to Human Factors" can be found at: www.fda.gov/cdrh/humfac/doitpdf.pdf.

use can be accomplished through discussions between the industry and the Human Factors Engineering Group during the device design and development phases. This approach would facilitate the review of PMAs and 510(k)s by permitting ODE's review scientists to focus their efforts on those aspects of the final device design that relate to safety and effectiveness or substantial equivalence, but would still ensure that human factors issues are addressed.

There are other postmarket controls to reduce premarket burden upon which the Agency may rely, such as postmarket surveillance. This control can be effectively used to address long-term safety and effectiveness issues. For example, when manufacturers wished to add a new type of porous coating to their hip implants, long-term safety and effectiveness could not be determined based on the available premarket data. Using a least burdensome approach, FDA cleared the devices with short-term data but required that postmarket surveillance be conducted on the implanted patients to address the long-term safety issues.

The MDR regulation is a control that allows FDA to monitor postapproval use of all medical devices, both 510(k) and PMA. This postmarketing control is used to alert the Agency to unanticipated events that may occur as a result of actual use situations, including interference with other products, use error, etc. This postmarket control could also help FDA and industry address concerns with new or modified devices going to market based on descriptive information and/or non-clinical testing.

Hyperlink #16

FDA and industry should make effective use of well-designed bench and/or animal testing. The testing should be designed to address a specific question, use standards or standardized test methods, employ scientifically relevant end-points, and use the most appropriate bench and/or animal model. For example, consider changes to the shape of the optic for an intraocular lens (IOL). For this type of device modification, there is well-established optical bench testing that serves as an accurate predictor of effectiveness for the particular optic design. As a second example, consider strength and fatigue testing that is used to assess certain aspects of the long-term performance of many orthopedic implants. This testing has been carefully designed to predict whether a particular implant design is able to withstand the stresses that the device will be subjected to over its useful life. Furthermore, this type of testing is well accepted by orthopedic device manufacturers and the Agency as a predictor of proper device design. Thus, the use of well-designed testing, such as that discussed in the above examples, helps to ensure that the relevant questions are satisfactorily addressed in the least burdensome manner.

Hyperlink #17

An effective use of incorporating by reference other premarket submissions, rather than re-submitting duplicative information, can be found in the IDE/PMA process. For almost all investigational devices, biocompatibility and/or bench testing is needed to support approval of an IDE. If this testing remains valid at the time the PMA is being prepared, that is, the investigational device was not modified during the course of the trial such that the testing would need to be repeated, the manufacturer could reference this testing in the PMA submission. This approach would also save review resources, since this information would not need to be re-

reviewed. For PMA supplements, industry should incorporate relevant data and information that have been previously submitted in the original PMA whenever possible, as discussed in the guidance document entitled,"Guidance for Industry -- Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review" (www.fda.gov/cdrh/modact/evidence.html). Similarly, if certain sections of an IDE (clinical protocol, case report forms, etc.) are relevant for a second IDE, the sponsor may wish to reference those sections rather than resubmit the information to the Agency. By incorporating as much information as possible, review resources will be conserved as well as preparation time on the part of the industry.

It should be noted, however, that there are certain cases in which resubmission of information may be more efficient than referencing a previously submitted file. For example, if an IDE has been closed, it would most likely be in the manufacturer's best interest to resubmit the needed sections of the closed IDE rather than have the reviewer try to access the file.

Hyperlink #18

Ensuring compliance with FDA statutes or regulations unrelated to the premarket decision (e.g., RCHSA, QS regulation) should be avoided. For example, consider the QS regulation. GMP issues should not affect substantial equivalence determinations in accordance with the new provisions of FDAMA. Under section 513(f)(5) of the act, FDA may not withhold a 510(k) determination because of a failure to comply with any provision of the act unrelated to a SE decision, including a finding that the facility in which the device is manufactured is not in compliance with GMPs (other than a finding that there is substantial likelihood that the failure to comply will potentially present a serious risk to human health).

Similarly, FDA should not attempt to verify compliance with laws and regulations administered by other federal agencies as a part of the clearance or approval decision. For example, manufacturers of medical devices must adhere to the regulations of the Occupational Safety and Health Administration (OSHA) when manufacturing their devices. While it is important for the safety of the worker that OSHA's regulations are followed, verifying conformance with them is not relevant to the SE or approval decisions. Consider, for example, that OSHA has its own guidelines to help protect operators of lasers and electrosurgical devices from "plume" in the healthcare setting independent of that which FDA requires for approval of these devices.

Having stated the above, it is important to note that while information about a device that does not relate to a premarket decision should not delay the Agency's clearance or approval decision, it may be appropriate for FDA to follow up on such information through other avenues. Therefore, if the Agency becomes aware of information that may represent non-compliance with its own or another agency's laws or regulations unrelated to premarket decision, FDA staff should follow up through appropriate channels.

Hyperlink #19

Often times during the course of the review of a document, FDA needs to obtain additional information from the submitter. Similarly, industry often needs to respond to these Agency

requests. In these situations, Agency staff and industry should follow the format outlined in the document entitled, "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA"[15] to help ensure that the requests and their responses are direct, concise, and complete.

Hyperlink #20a

A recent draft guidance document for modifications to intraocular lenses, a well-understood implantable device, illustrates the sound application of the least burdensome principles. This document identifies the requirements for establishing the safety and effectiveness for a wide variety of potential device modifications. Based on the potential impact of a given modification, the modified device may be marketed based on:

- No prior approval required (the validating information is summarized in the PMA annual report);
- Non-clinical data;
- Limited, confirmatory clinical data; or
- Full clinical study (equivalent to that for new device).

Hyperlink #20b

Under a new amendment to the IDE regulation (21 CFR 812.35(a)(3)), sponsors may make certain modifications to their device design/manufacturing process and/or their clinical protocol without prior FDA approval of a supplement if the changes are reported to the Agency within 5 days of implementation. For design/manufacturing modifications, the change must not affect the basic principles of operation of the device or otherwise be a significant change. To help sponsors decide if a proposed change meets these statutory criteria, the regulation recommends that sponsors use design controls, preclinical/animal testing, peer reviewed published literature, or other information such as preliminary results of their clinical trial or marketing experience gained outside the US. Protocol changes that do not affect the rights, safety or welfare of the subjects, scientific soundness of the investigational plan, validity of the data, or the risk to benefit relationship may also be made without prior FDA approval. Similar to the device modifications, the sponsors should use peer reviewed published literature, preliminary results of their clinical trial or marketing experience gained outside the US, or the recommendations of their clinical investigators to support the protocol changes. Sponsors are encouraged to discuss proposed changes with the Agency if there is any question about whether the protocol change might affect scientific soundness of the plan or the validity of the data.

By allowing IDE sponsors to proceed with certain types of device design/manufacturing and protocol changes without prior FDA approval of an IDE supplement, the regulatory burden on IDE sponsors should be reduced. Furthermore, the alternative approaches provided to IDE sponsors in the regulation exemplify the sound application of the least burdensome principles.

[15] This guidance is available at: www.fda.gov/cdrh/modact/guidance/1195.html